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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,795	04/23/2001	Erin E. Murphy	SF0818KQ	5250

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,795	MURPHY ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15, 21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15, 21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11-15, 21 and 22 are pending in the instant application. Claims 11 and 12 have been amended as requested by Applicant in the Paper filed Dec. 17, 2003.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 11-15, 21 and 22 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous Office Action, Paper No. 8, at pages 4-7, Paper No. 13 at pages 3-8, and below.

It was agreed from the telephone interview of November 24, 2003, that the remaining basis supporting this rejection is the assertion that the mRNA data disclosed in the specification does not support a specific and substantial utility or a well established utility because mRNA expression does not necessarily predict protein expression, and Applicants in their response address this issue.

Applicants traverse the rejection and submit that there is no evidence that mRNA expression detected via traditional means, e.g., in situ hybridization, does not predict or correlate with protein expression, and that mRNA detection technology has improved dramatically allowing detection of mRNA that is expressed as a single copy per cell (Exhibit B). Applicants on page 7 of the response submit that the data in the Haynes et al. review is incomplete, lacks a statistical analysis of the correlation between mRNA and protein expression in Figure 1, and that one of ordinary skill in the art would find the assertions of Haynes et al. speculative in the absence of more rigorous analysis. Applicants submit that the paper of Gygi et al. (Exhibit B, "the MCB paper") provides a more thorough analysis of the data, and supports the traditional dogma regarding the positive correlation between mRNA expression for highly expressed mRNA transcripts. Applicants submit that after examining more genes with a strikingly similar expression profile to that profile first reported in the Haynes review (106 as opposed to 80 in Haynes), the authors conclude that the was a general trend of increases protein levels resulting from increased mRNA levels, and that this correlation coefficient for this general trend was 0.935 (Exhibit B, Fig. 5). Applicants note that both the Haynes paper and the MCB paper indicate that the greatest variance in the correlation between mRNA and protein expression occurs in the subset of mRNA transcripts at a low copy number, i.e., 10 copies or less per cell, a subset of mRNA transcripts at or below the detection limits of in situ hybridization analysis employed in the instant specification. Applicants assert that the detection limits of in situ hybridization analysis makes it difficult to routinely detect mRNA transcripts present at 10 or less copies per cell, and thus it is questionable whether this subset of transcripts (10 copies or less) is even detectable in the in situ hybridization analysis employed in the instant application.

Applicants assert that while there is only an inexact correlation between mRNA and protein expression seen for the low mRNA copy subset, the range in protein expression resulting from this subset is still well below that observed within the high mRNA copy subset. Applicants further submit that neither the Haynes review or the MCB paper provides evidence or suggests that a high copy transcript does not result in high protein expression.

Applicants' arguments and references have been fully considered but are not deemed persuasive. Analysis of the Haynes et al. and MCB papers shows that there is a positive correlation between only the most abundant mRNAs and protein expressed. However, the correlation coefficient for the whole data set of the MCB paper, 0.935, was highly biased by a small number of genes with very large protein and message levels (page 1726). Genes for which the message level was below 10 copies per cell and included 69% (73 out of 106 genes) of the data used had a correlation coefficient of only 0.356. The MCB paper also found that levels of protein expression coded for by mRNA with comparable abundance varied by as much as 30-fold and that the mRNA levels coding for proteins with comparable expression levels varied by as much as 20-fold. As shown in Figure 6, the correlation value remained relatively stable in the range of 0.1 to 0.4 if the lowest expressed 40-95 proteins used in the study were included, but the correlation value steadily climbed by the inclusion of each of the 11 very highly expressed proteins. Therefore, the MCB paper supports a positive correlation between mRNA expression and protein abundance only with **very highly** expressed mRNAs. The issue at hand in the instant application is whether protein is elevated and such elevation is detectable and correlative with a disease or disorder. Applicants' appear to argue that the mRNA of the instant invention, based on the MCB paper and because it can be detected by in situ hybridization, belongs to this

class of very highly expressed mRNA. The most highly expressed class of mRNAs, from the Haynes et al. and MCB paper, appear to constitute approximately 10-15% of the total mRNA. The instant specification teaches that the RANKL message can be detected in three days of autogradiograph exposure of mRNA from allergic guinea pig and monkey lungs, while it takes a 14 day exposure in mRNA from normal lungs, an approximately 5 fold increase in expression. There is no information provided that would support that detection of a mRNA after a three day autoradiographic exposure correlates with RANKL mRNA belonging to the class of very highly expressed mRNAs, or that a five-fold increase in mRNA level would correlate with a similar increase in protein expression. Absent this correlation, it cannot be assumed that the RANKL message in diseased lungs belongs in this category, or that there is a difference in expression of the RANKL protein between normal or diseased lungs. Additionally, post-translational effects are extremely important in determining protein levels, and this was not considered in the analysis of the data in Haynes and the MCB paper. In the abstract of the MCB paper, it is stated:

> "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed for some genes, while the mRNA levels of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold.....Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient."

For these reasons, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11-15, 21 and 22 also remain rejected under 35 U.S.C. 112, first paragraph, for reasons of record in the previous Office Action, Paper No. 8, at page 7, and Paper No. 13, at page 8. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102 and § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

5. Claims 11-14, 21 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Goddard et al., U.S. published application 20030092044, effective filing date April 12, 1999 (60/128,849), and claim 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Goddard et al., U.S. published application 20030092044, and further in view of Akita et al., US Patent No. 5,968,511, for reasons of record in the previous Office Action, Paper No. 13, at pages 9-11.

Applicants traverse the effective priority date assigned the instant application and asset the because the disclosed nucleic acid sequences at a minimum meet the utility requirements under 35 USC § 101 and enablement under 35 USC § 112 in view of the disclosed in situ

hybridization data, and the in situ hybridization data was disclosed in provisional application 60/099,999, filed Sept. 11, 1998, Applicants should receive benefit of priority under 35 USC § 119(e) to this application, and therefore the Goddard and Akita references are not proper references under 35 U.S.C. 102(e) of 35 U.S.C. 103(a).

Applicants' arguments have been fully considered but are not deemed persuasive. The nucleic acid sequences receive benefit under 35 USC § 119(e) to provisional application 60/099,999 because they are enabled for use under 35 USC § 112. However, the instant claims are directed to protein binding compounds of the expressed protein, and the protein is not enabled for use under 35 USC § 112 in the instant application or the provisional application for the reasons discussed above. Therefore binding compounds are not enabled for use under 35 USC § 112. The effective priority date of the claimed invention is the filing date of the parent 09/351,777, since the instant application is a continuation of 09/351,777. For these reasons, the rejections are maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

6. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

Official papers Before Final and After Final filed by RightFax should be directed to (703) 872-9306.

The customer service RightFax number is (703) 872-9305.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Eileen B. O'Hara, Ph.D.

Patent Examiner

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600